This article provides an overview of the benefits of filling two-piece hard gelatin capsules with liquids. It discusses formulation requirements, compares two-piece hard capsules to softgels, and offers strategies for liquid filling. It also describes one company's approach to manufacturing capsules and its method for sealing the filled capsules.

 encapsulated liquids have demonstrated their commercial viability, and the scientific literature documents several of the milestones that have been attained over the years in this area. One such milestone was increasing the bio-availability of digoxin. It was first formulated as a softgel in 1977 [1], and by 1980, Walker et al. had demonstrated that a thixotropic formulation could be filled into two-piece hard gelatin capsules [2].
In 1981, Sandoz brought to market Sandimmun, a coarse emulsion of cyclosporine A [3]. But that product’s variability in delivering the active pharmaceutical ingredient (API) led to its reformulation into a self-emulsifying drug delivery system (SEDDS) of cyclosporine A in 1988, and it was marketed as Neoral [4, 5]. In 1995, Bristol-Myers Squibb introduced a thixotropic, sustained-release formulation (captopril) as a liquid-filled two-piece hard capsule [6,7].

Likewise today, research and development efforts focus on the many advantages that liquids can provide to challenging compounds. In fact, many pharmaceutical companies dedicate research groups to investigating liquid formulations. Usually the goal is to overcome poor aqueous solubility to improve oral bio-availability; poor content uniformity of low-dose drugs; and safety concerns when handling highly potent APIs, such as cytotoxins.

While there are several new methods for delivering APIs (i.e., transdermal, intranasal, and inhaled technologies), the number of products on the market that use these technologies is small, and the preferred route of delivery remains solid oral dosage forms. That explains why the drive to encapsulate liquids in two-piece hard gelatin capsules is increasing: Companies want to expand the number of products they can offer in solid dosage form, and encapsulating liquids is sometimes the best or only option.

**The role of liquids in today’s formulations**

Liquid formulation strategies can address problems in many areas [8]. The introduction of new drug discovery technologies, such as high-throughput screening and combinatorial chemistry, has generated libraries of new compounds with higher molecular weight and greater lipophilicity than compounds discovered using traditional methods [9]. Therefore, it is not surprising that, of all the applications for liquid-filled two-piece hard capsules, increasing the bio-availability of poorly soluble compounds attracts the most interest.

Lipophilic solutions [10, 11] and solid dispersions [10, 12] are two means of dealing with poorly soluble compounds. Excipient suppliers now provide a host of liquid and semi-solid excipients to help solubilize APIs for improved delivery. The importance of these excipients is evident in Figure 1, which compares the in vitro dissolution profiles of triamterene when formulated with different solubilizing excipients [13]. Formulating drug compounds in liquid or semi-solid excipients is also used to target lymphatic transport [14] or to circumvent the impact of transporters [15] and metabolizing enzymes [16] in the GI tract.

The major technique for enhancing bio-availability is SEDDS [10, 16, 17, 18], a technique that uses lipophilic, pre-concentrated solutions of the API and excipients (typically a liquid carrier, a surfactant, and a co-surfactant). When delivered to the aqueous environment of the GI tract, the SEDDS spontaneously forms an oil-water emulsion that contains particles smaller than 200 nanometers. Selecting compounds that are candidates for SEDDS requires determining the essential properties of the API. Benameur provided an excellent summary of the properties to focus on [19].

Low-dose compounds can also benefit from liquid encapsulation. When a true solution exists, the API is inherently uniformly dispersed throughout the formulation [20]. And because filling two-piece hard capsules with liquids has been demonstrated to provide good accuracy [21], proper dosage through a simple formulation is ensured. This is especially important when formulating with high-potency compounds because the dose is often small. Furthermore, when a high-potency API and/or cytotoxic compound is dissolved in liquid, dusting diminishes drastically, which decreases the risks of cross-contamination and employee exposure. Bowtle demonstrated this by swab-testing capsule bushings on a machine that filled liquids into hard capsules [22].

Low-melting-point compounds are also suitable candidates for liquid filling. The low-melting-point drug can be dissolved in a single liquid vehicle and encapsulated. When these types of compounds are formulated as a powder for encapsulation or compression into a tablet, they typically require high excipient loads to process reliably.

Figure 1

Comparison of dissolution profiles of triamterene formulated with different solubilizing excipients [13]
dence to the encapsulation of liquids. Technology to assist both research and manufacturing groups with liquid filling has evolved from difficult-to-operate, capital-intensive equipment to the point that small, lab-scale liquid filling and sealing units are commercially available. Formulation technology and equipment have evolved in step with the pharmaceutical industry’s need to deliver the poorly soluble compounds that have become predominant in product pipelines.

Assessing the compatibility of fill materials

The properties of the API dictate whether it is a good candidate for liquid filling. Next, suitable excipients are evaluated, with an understanding that neither the API nor the excipients should cause the gelatin shell to gain or lose excessive moisture, which can cause the shell to lose its mechanical strength. All substances must also be chemically compatible with gelatin [23].

To maintain flexibility, the capsule shell must retain a moisture content of 13 to 16 percent. Below that range capsules become brittle and are prone to breakage. Above that range the capsules may deform. To measure the moisture exchange between the fill material and the shell, fill the capsules with the product in question and store them at different levels of relative humidity (RH) (i.e., 2.5, 10, 30, 50, and 60 percent) for 2 weeks. During that period, the water exchange across the range of RHs should not exceed ±2 percent. Fill materials that exchange more than ±2 percent moisture compared to empty shells stored under the same conditions are not suitable for liquid filling. The capsule’s mechanical resistance must be checked in relation to moisture content. This entails storing the filled capsules for 1 week at different RHs and then testing them for resistance to breakage and deformation.

Chemical compatibility of the fill material with the gelatin shell is also important. For instance, if the fill material causes the protein chains of the gelatin to cross-link, there may be a delay in dissolution. One method of monitoring cross-linking is to first store the fill material inside the hard gelatin capsules under ICH accelerated storage conditions (40°C at 75 percent RH), and then replace the fill material with acetaminophen. Next, conduct a dissolution test according to USP guidelines to compare the dissolution profiles of the filled and unfilled capsules stored at the accelerated conditions. Table 1 lists some liquid and semi-solid excipients that are compatible with hard gelatin capsules.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Liquid excipients for hard gelatin capsules</td>
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<tr>
<td><strong>Lipophilic vehicles</strong></td>
</tr>
<tr>
<td>Refined oils:</td>
</tr>
<tr>
<td>Arachis oil, Castor oil, Cottonseed oil, Corn oil, Olive oil, Sesame oil, Soybean oil, Sunflower oil</td>
</tr>
<tr>
<td>Medium chain triglycerides/esters:</td>
</tr>
<tr>
<td>Akomed E, Akomed R, Labrafac CC, Labrafac PG, Lauroglycol FCC, Mighyols (810, 812, 829), Softisan 845</td>
</tr>
<tr>
<td>Semi-solid lipophilic vehicles</td>
</tr>
<tr>
<td>Aerosil, Cetosteryl alcohol, Cetyl alcohol, Gelucires (33/01, 39/01, 43/01), Steryl alcohol, Softisans (100, 142, 378, 649), Glyceryl palmitostearate, Hydrogenated refined oils</td>
</tr>
<tr>
<td>Solubilizing agents, surfactants, and emulsifiers</td>
</tr>
<tr>
<td>Capryol 90, Cremophor RH 40, Gelucires (44/14, 50/13), PEGs MW &gt; 4000, Tween 80, Softigel (701, 767), Lauroglycol 90, Labrafils (M 1944 CS, M 2125 CS)</td>
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<tr>
<td>Excipients incompatible at 100%</td>
</tr>
<tr>
<td>MCMs (Akoline, Capmul, Imwitor 308), PEGs MW &lt; 4000, Glycerin, Propylene glycol, Transcutol P, Span 80, Ethanol</td>
</tr>
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</table>

First, soft gelatin contains a significant amount of plasticizer, usually glycerol or sorbitol, while the gelatin used in hard capsules contains no plasticizer. Plasticizers impart elasticity to the gelatin shell and allow it to accommodate a wide range of hydrophilic excipients, but their presence raises the issue of component migration. For example, if the plasticizer solubilizes the compounds of the formulation, those compounds can migrate into the soft gelatin shell. (The large amount of water in the gelatin during softgel manufacture may also play some role in this migration.) Conversely, the plasticizer might migrate into the formulation.

Furthermore, soft gelatin may expose the fill material to more oxygen than a hard capsule would because the plasticizers in soft gelatin create channels that are larger than those in hard gelatin. See Figure 2. Greater exposure to air increases the potential for oxidizing (degrading) the fill material. In addition to an inherently lower oxidation potential, hard gelatin capsules can be filled in a nitrogen environment to further protect the contents. The smaller channels in hard gelatin capsules also mask the off-tastes and odors associated with pharmaceutical formulations better than softgels can.

Hard capsules vs. softgels

No discussion of filling hard gelatin capsules with liquids is complete without a comparison to soft gelatin capsules. There are significant differences between the dosage forms, and it’s sometimes helpful to consider them complementary rather than competitive. Actually, the formulation often dictates the capsule type, but in cases where the formulation allows a choice between dosage forms, hard capsules have several advantages over softgels because they are less complex to manufacture.

**Figure 2**

Soft gelatin (right) has larger channels than hard gelatin, as shown in these freeze etchings taken from a scanning electron microscope (1.6 x 10^4 magnification).
Manufacturing softgels is also very different from filling hard gelatin capsules with liquids. Empty hard gelatin capsules are purchased separately and then filled. With softgels, two ribbons of gelatin come together in a die to form the capsule, which is filled and sealed in one continuous process. Furthermore, the softgel process cannot accept fill materials that exceed 35°C. And formulations containing large particles or fibrous materials are not good candidates for softgels because they may prevent a secure seal when the two sides of the shell come together.

Another potential drawback: Liquid formulations may require a formulation of the softgel shell itself. If this is contracted out to a softgel manufacturer, intellectual property rights to the shell typically remain with the contract manufacturer. That limits the possibility of changing to another contractor. In general, softgel manufacture requires expensive equipment and is a labor-intensive process. For the development of soft gelatin capsules, contract manufacturers often require several kilograms of formulation, which can be challenging in the early development phase when large amounts of the drug substance are difficult to acquire. With hard gelatin capsules, small-scale filling with only a few grams of formulation can be done in-house with lab-scale equipment. No lab-scale (benchtop) equipment for softgel production exists today.

**Table 2**

<table>
<thead>
<tr>
<th>Size</th>
<th>000el</th>
<th>0</th>
<th>00el</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>130</td>
<td>118</td>
<td>110</td>
<td>96</td>
<td>76</td>
<td>61</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Tolerance (mg)</td>
<td>±10</td>
<td>±7</td>
<td>±7</td>
<td>±6</td>
<td>±5</td>
<td>±4</td>
<td>±3</td>
<td>±3</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>1.02</td>
<td>0.91</td>
<td>0.7</td>
<td>0.68</td>
<td>0.5</td>
<td>0.37</td>
<td>0.3</td>
<td>0.21</td>
</tr>
<tr>
<td>Available Volume (ml)</td>
<td>0.89</td>
<td>0.82</td>
<td>0.61</td>
<td>0.59</td>
<td>0.43</td>
<td>0.33</td>
<td>0.26</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**A capsule for liquids**

While many companies are opting for liquid encapsulation today, it isn’t exactly a new trend. In 1998, Capsugel launched a capsule specially designed for liquid and semi-solid fills [24]. See Figure 3. This capsule is longer than standard capsules, so that when the capsule body and cap are fully joined, the top of the capsule body's wall contacts the interior of the cap. This provides the primary barrier to prevent the liquid fill from escaping. (It is essential to keep the area of the cap-body interface uncontaminated by fill material. Otherwise, it is virtually impossible to seal the capsule.) To further prevent or reduce leakage and contamination at the cap-body interface, the capsule has no side air vents, which are typical of capsules used in high-speed powder filling. The capsule is normally filled to no more than 90 percent of its volume to minimize the chance of the liquid fill contaminating the cap-body interface. Table 2 lists available volume and other properties of two-piece capsules for liquid filling.

**A brief comparison of sealing methods**

Once closed, the capsule must be sealed to prevent leaks and tampering. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing [25]. See Figure 4.

This fusion process begins with an application of less than 50 microliters of sealing solution to the cap-body interface. The solution penetrates the overlapping cap and body by capillary action, while a vacuum removes any excess sealing fluid from the capsule. Next, gentle application of warm (40°C to 60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution. The entire process takes less than 1 minute and transforms the two-piece hard capsule into a leak-free dosage unit. Once sealed, the capsule meets tamper-evidence guidelines since it cannot be opened without visibly altering it.
Another method entails banding the cap-body interface with a thin strip of gelatin. Banding, however, involves several additional tasks compared with hydroalcoholic sealing. First, someone must prepare the gelatin bath, and its viscosity must be checked continuously. Operators must also address the risk of microbiological contamination associated with warm liquid gelatin. Furthermore, the gelatin band can cause physical defects in the capsule: Bubbles may form in the gelatin band or the capsules may take on a “banana” shape. The deformation usually occurs when the warm band of gelatin cools and the capsules are subjected to a long drying cycle.

The photos above show liquid filling and sealing equipment. The GMP-compliant lab-scale filler-sealer fills and seals as many as 1,200 capsules per hour [26]. It is well suited to conducting R&D and making early clinical trial supplies. It can handle thixotropic and hot-melt fill materials. The other machine is a commercial-scale dedicated capsule sealer that links to high-speed filling machines via a belt conveyor [27]. It seals as many as 60,000 capsules per hour and has proven itself in both the pharmaceutical and the dietary-supplement markets [28].

Conclusion

Liquid formulations filled into two-piece hard capsules have attracted substantial interest in the pharmaceutical industry over the last decade. Today’s challenges in product development due to the poor aqueous solubility and high potency of the new molecular entities are being addressed by several development groups that are focused on liquid or semi-solid formulations.

With today’s equipment, filling and sealing these formulations into two-piece hard gelatin capsules can be done easily in-house. The processes have also been proven to be commercially viable for in-house manufacturing. Several pharmaceutical products currently under development are expected to reach the market within the coming years, increasing the number of commercial products using a liquid-filled and sealed capsule.

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